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Full title: Prognostic risk modelling for patients undergoing major lower limb amputation: an analysis of the UK National Vascular Registry.

Running head: Operative risk after major lower limb amputation

Authors:

Graeme K Ambler; PhD, MRCS; Bristol Centre for Surgical Research, University of Bristol and North Bristol NHS Trust, Southmead Hospital, Southmead Road, Bristol, BS10 5NB.

Emma Thomas-Jones; PhD; Centre for Trials Research, Cardiff University, 7th Floor, Neuadd Meirionnydd, Heath Park, Cardiff, CF14 4XW

Adrian GK Edwards; MRCP, FRCGP, PhD; Division of Population Medicine, Cardiff University, 8th Floor, Neuadd Meirionnydd, Heath Park, Cardiff, CF14 4XW

Christopher P Twine; MD; Bristol Centre for Surgical Research, University of Bristol and North Bristol NHS Trust, Southmead Hospital, Southmead Road, Bristol, BS10 5NB

Correspondence:

Graeme K Ambler

Bristol Centre for Surgical Research

Canynge Hall
39 Whatley Road
Bristol
BS8 2PS

Telephone: +44 117 331 3929
Email: Graeme.ambler@bristol.ac.uk

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What does this study add to the existing literature and how will it influence future clinical practice?

This observational study used data from the UK National Vascular Registry to look at risk factors for in-hospital mortality and morbidity following major lower-limb amputation. Eleven independent risk factors were identified including emergency admission, raised white cell count or creatinine, low albumin or patient weight, age, American Society of Anesthesiologists grade, amputation level and prior intervention to the amputated limb. A risk model was developed which had excellent calibration and good discrimination (C-statistic 0.79, 95% C.I. 0.77-0.80). An on-line calculator for the model is available, making it easy to use.

Abstract

Objective: Major lower limb amputation is the highest-risk lower limb procedure in Vascular Surgery. Despite this, few high-quality studies have examined factors contributing to mortality. We aimed to identify independent risk factors for peri-operative morbidity and mortality and develop reliable models for estimating risk.

Methods: All patients undergoing lower-limb amputation above the ankle entered into the UK National Vascular Registry (January 2014–December 2016) were included. Missing data were handled using multiple imputation. Models were developed to evaluate independent risk-factors for mortality (the primary outcome) and morbidity using logistic regression, minimising the Bayesian information criterion to balance complexity and model fit. Ethical approval for the study was granted (Wales REC 3 ref:16/WA/0353).

Results: All 9549 above ankle joint amputations in the registry were included. Overall, 865 patients (9.1%) died before leaving hospital. Independent factors associated with mortality were emergency admission, bilateral operation, age, American Society of Anesthesiologists grade, abnormal electrocardiogram and increased white cell count or creatinine ($P<0.01$ for all). Independent factors reducing mortality were trans-tibial operation, increased albumin or patient weight, and previous ipsilateral revascularisation procedures ($P<0.01$ for all). A risk model incorporating these factors had good discrimination (C-statistic 0.79, 95% C.I. 0.77-0.80) and excellent calibration.

Morbidity rates were high, with 6.6%, 9.7% and 4.3% of patients suffering cardiac, respiratory and renal complications respectively. The risk model was also predictive of morbidity outcomes (C-statistics 0.74, 0.69 and 0.74 respectively).

Conclusions: Morbidity and mortality after lower limb amputation are high in the UK. We identified some potentially modifiable factors for quality improvement initiatives and developed accurate predictive models that could assist patient counselling and decision-making.

Key words: Amputation; Peripheral vascular disease; Mortality; Risk modelling

Introduction

Major lower limb amputation is one of the highest risk surgical procedures in the UK, with in-hospital mortality rates of approximately 6% for below- and 12% for above-knee amputation.[1] While this is largely related to patient fitness rather than operative complexity, it is nonetheless important, therefore, to identify prognostic factors contributing to mortality rates so that quality improvement programmes can be implemented. Although limited work exists for UK populations, the only large studies come from parts of the world with radically different healthcare systems, calling generalisability into question (Supplementary Table 1).[2-7]

Mortality is not the only negative outcome experienced by this cohort; they face long hospital stays, a high rate of perioperative complications and frequent readmissions.[8] Prognostic risk modelling into leading causes of morbidity is therefore also important. Individualising consent[9] and risk adjustment of surgeon specific outcome data[10] are also enabled by robust risk models. There is some evidence that the broad adoption of the EUROSCORE[11] risk prediction tool in cardiac surgery helped lead to the dramatic improvement in cardiac surgical outcomes which occurred around the turn of the millennium.[12] It is possible that by facilitating appropriate targeting of resources to higher risk patients it may be possible to replicate these results in other fields. Thus development of accurate risk models for patients undergoing major lower limb amputation may have a multitude of benefits.

The objectives of this study were therefore to identify the independent risk factors for perioperative mortality and leading causes of morbidity in UK patients and develop robust prognostic models. The ability of these models to accurately predict mortality in a contemporary UK dataset were then compared to previously published models.

Methods

Data

All patients recorded in the UK National Vascular Registry (NVR) as undergoing major lower limb amputation (below knee, through knee, above knee, hip disarticulation and hind quarter amputation) from January 1 2014 until December 31 2016 were included in the study. Data were formally requested through and approved by the UK Healthcare Quality Improvement Partnership, who are the data controllers for English and Welsh data within the NVR; and through the Audit and Quality Improvement Committee of the Vascular Society of Great Britain and Ireland, who are the data controllers for Scottish and Northern Irish data within the NVR. Data were retrieved in March 2018 to allow time for completion of the index admission as well as data entry from sites.

A list of the variables applied for and their type is given below in Supplementary Table 2.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes were return to theatre during admission, re-admission to a higher level of care, post-operative length of stay and post-operative complications (subdivided into several different categories: cardiac, respiratory, cerebral (stroke), renal failure, haemorrhage and limb ischaemia).

Ethical approval and study registration

The study was approved by Wales Research Ethics Committee 3 (reference number 16/WA/0353), and the protocol was registered in the Australia and New Zealand Clinical

Trial Registry (ANZCTR) as ACTRN12618000356268. This report has been prepared in accordance with the STROBE and TRIPOD statements.[13,14]

Statistical methodology

All statistical analysis was performed in the R statistical programming environment version 3.5.1.[15] Multiple imputation using the *mice* package version 3.3.0 was used to handle missing data,[16] excluding parameters with more than 50% of values missing from multivariate modelling. Data were imputed using 45 replicates with 45 iterations of the chained equations algorithm for each replicate. In order to explore differences there might be between analysis based on the imputed data and the unimputed data, a sensitivity analysis was done by performing univariate analysis using both complete case analysis compared with the multiply imputed data.

Univariate analysis was performed using univariate logistic regression, together with application of Rubin's rules to pool estimates for multiple imputation.[17] Continuous variables were kept as such and odds ratios are given per unit change in value rather than dichotomised into 'high' and 'low' values. Multivariate analysis was performed using multivariate logistic regression analysis to develop models using pre-operative predictors. Parameters were selected for inclusion in prognostic models using stepwise selection and following an Information Criterion based analysis, by minimizing the Schwarz-Bayes Criterion.[18] This was done separately for each of the 45 replicates and terms which were present in at least half of the replicates were retained. The National Vascular Registry was deliberately designed as a fairly minimal reporting set in response to high rates of missing data in the previous national registry, which included a large number of parameters, so that all recorded predictors are felt to be potentially important for outcomes. We therefore evaluated all of the predictors listed in Supplementary Table 2 which had missing data levels less than 50% for inclusion in the prognostic models. ROC curve analysis was used to assess model discrimination using the *pROC* package version 1.12.1.[19] The Delong method was then used to calculate confidence intervals for the area under the ROC curve (C-statistic) and test whether performance was different to the estimated C-statistics of existing models.[20] Comparison with existing models is hampered by the fact that three of the four models we found in a literature search include terms which are not recorded in the National Vascular Registry, so any estimation of the discriminatory power of these models will be hampered by the fact that we can only set these parameters to default values.[2,5,7] The revised Vascular Biochemistry and Haematology Outcome Model does not suffer from this problem, so comparison with this model can be viewed as 'fair'.[3] The Hosmer-Lemeshow goodness of fit test was used to assess calibration of the models.[21]

Results

Demographics and outcomes

There were 12,593 amputations entered into the registry during the study period, of which 9549 were above the ankle and so comprised the study population. Of these, 4516 (47%) were trans-tibial, 4369 (46%) trans-femoral, 442 (5%) through-knee, 32 (0.3%) hip disarticulation and 190 (2%) were simultaneous bilateral procedures. Table 1 summarises the baseline characteristics of the study population, together with the amount of missing data for each parameter.

Overall, 865 patients (9.1%) died before leaving hospital. The mortality rate for below knee amputations (5.8%) was lower than for above knee procedures (12.0%; P<0.0001). Data were not available on cause of death or re-amputation rates. There was also a high rate of post-operative morbidity in the cohort, with 6.6%, 9.7% and 4.3% of patients suffering cardiac, respiratory and renal complications respectively. Less than 1% of patients was recorded as having a post-operative stroke or bleeding complication, and 4.4% had a complication relating to limb ischaemia. Ten percent (966/9546) of patients had an unplanned return to theatre, while 4% (363/9545) were re-admitted to critical care. The median post-operative length of stay was 16 days (IQR 9—28 days), with an overall median length of stay of 24 days (IQR 14—42 days).

Risk factors for post-operative mortality

Univariate analysis revealed that increased patient age; a history of ischaemic heart disease, congestive heart failure, chronic lung disease, chronic kidney disease or stroke; a raised white cell count, raised serum creatinine or low serum albumin; an abnormal ECG; increased American Society of Anaesthesiologists (ASA) grade; emergency admission and pre-operative beta-blocker therapy all increased the odds of in-hospital mortality. Male sex, previous intervention on the same side, below knee amputation, current smoking, statin or ACE inhibitor/ARB therapy, and increased weight all had protective effects (Table 2).

Analysis was repeated using complete case analysis to assess sensitivity to the imputation methodology. Results were almost identical to the multiple imputation analysis, giving confidence that the imputation methodology had not introduced significant bias (Table 2).

Multivariate regression modelling revealed that independent factors associated with worse in-hospital mortality were emergency admission (Odds Ratio (OR) 2.47, 95% Confidence Interval (C.I.) 1.89-3.24), bilateral operation (OR 2.19, 95% C.I. 1.48-3.25), age (OR per 10 year increase 1.21, 95% C.I. 1.13-1.29), ASA grade (OR per unit increase 2.60, 95% C.I. 2.27-2.98), abnormal ECG (OR 1.52, 95% C.I. 1.28-1.79), and increased white blood cell count (OR per 10^9 cells/L increase 1.02, 95% C.I. 1.01-1.03) or serum creatinine (OR per 10 μmol/L increase 1.02, 95% C.I. 1.02-1.03).

Independent protective factors reducing in-hospital mortality were trans-tibial operation (OR 0.61, 95% C.I. 0.52-0.72), increased serum albumin (OR per g/L increase 0.97, 95% C.I. 0.95-0.98), previous procedures to the amputated limb (OR 0.79, 95% C.I. 0.68-0.92), and increased patient weight (OR per 10kg increase 0.95, 95% C.I. 0.91-0.99).

Development of a prognostic model of post-operative mortality

A multivariate logistic regression model using the factors identified above to predict the chances of surviving to hospital discharge was constructed. Hosmer-Lemeshow goodness of fit analysis revealed good model fit (P=0.348 for evidence of mis-calibration). A calibration table is given in Supplementary Table 3, along with details of the model formula. This is displayed graphically in the Supplementary Figure.

ROC curve analysis showed that the model (labelled 'UKAmpRisk') has good (bordering on excellent) discrimination (C-statistic 0.79, 95% C.I. 0.77-0.80). A plot of the ROC curve is shown in Figure 1.

Comparison to existing models

The C-statistic was 0.59 (95% C.I. 0.56-0.61) for the Vascular Biochemistry and Haematology Outcomes Model (VBHOM),[2] 0.65 (95% C.I. 0.63-0.67) for the revised VBHOM model (VBHOM2),[3] 0.68 (95% C.I. 0.66-0.70) for the Veterans Affairs Model (VAM),[7] and 0.65 (95% C.I. 0.64-0.68) for the National Surgical Quality Improvement Programme (NSQIP) model.[5] All four models showed inferior discrimination to our model (P<0.0001 for all comparisons). Figure 1 shows all five ROC curves on the same graph for comparison. The NSQIP, VBHOM and VBHOM2 models all failed the Hosmer-Lemeshov goodness of fit test (P<0.0001 in each case), suggesting that they are also poorly calibrated for this patient cohort. The intercept coefficient was not published for the VAM model, so it was not possible to assess the calibration for that model.

Risk factors for secondary outcomes

Multivariate regression modelling revealed that low serum albumin and high ASA grade were consistent predictors of most morbidity outcomes. Other predictors frequently associated with outcome were amputations done as an emergency and a raised serum creatinine level. Full details of the parameters which were independently associated with the secondary outcomes are given in Supplementary Table 4. The ability of models based on these factors to discriminate between patients who did or did not suffer these morbidity outcomes was again assessed using the C-statistic (Supplementary Table 4).

The predictive model for in-hospital mortality was again a good predictor of several of the morbidity outcomes including cardiac, respiratory and renal complications (C-statistics 0.74, 0.69 and 0.74 respectively).

Discussion

We have identified eleven factors which are independently associated with in-hospital mortality in patients undergoing major lower-limb amputation. While some of these factors (principally age and ASA grade) are not modifiable, the majority are potentially amenable to modification through improved clinical care.

Many, such as emergency admission and a raised white cell count, are linked to management of patients at a late stage in their disease and may reflect late presentation or recognition. This highlights the critical role of healthcare staff to recognise the deteriorating foot in the community, and robust in-hospital systems and teams to treat patients quickly. Earlier recognition will reduce the number of patients undergoing amputation as an emergency when they are septic, with increased risk of both kidney and cardiac dysfunction, often following a period of chronic low-grade foot sepsis resulting in malnutrition and low albumin. Amputation is often followed by long periods in hospital. In our experience, much of this time is as a result of social or organisational factors, including the need to assess a patient's home for wheelchair suitability and carry out any necessary modifications. Earlier recognition would allow amputation to be handled in a more elective manner, so that this could be done ahead of time, facilitating shorter hospital admissions and thus reduced healthcare costs. Such systems are already in place for many patients in the form of the diabetic foot service and could be rolled out to all patients with chronic limb-threatening ischaemia. Evidence is already emerging that such 'limb-salvage' services can make an impressive impact by reducing amputation rates.[22] However the present work highlights the fact that limb salvage must not be the only measure of the success of 'limb-salvage' services. Early recognition that limb salvage is unlikely to succeed could facilitate early discussion about the options and outcomes of amputation – indeed there is increasing recognition of this fact from those running limb-salvage services.[23] This in turn could improve the outcomes of those patients who decide to have an amputation rather than continuing to pursue efforts at limb salvage which are likely ultimately to be unsuccessful.

Some of these patients are frail and with co-existing cognitive impairment they may benefit little from amputation. Early recognition of the deteriorating limb will help to prompt conversations about whether amputation is something the patient would want or benefit from, allowing decisions about active or palliative management to be made based on accurate prognostication.

We have also developed a model which could be used to aid counselling and decision-making, either in clinic or at the bedside, by quantifying the probability of the patient surviving to hospital discharge. We have developed a web calculator for easy use in clinic which is available from www.ambler.me.uk/Vascular, and could easily be converted into a standalone smartphone app for offline use. By having a model which can more reliably predict mortality, discussions about options can be more fully explored with patients, enhancing shared decision-making.[24] Multiple previous studies have shown that surgeons systematically underestimate the chances of a patient surviving an operation.[25,26] As the choice between amputation and conservative management is sometimes the choice between amputation and palliation, it is critically important that these discussions are conducted in the context of reliable risk estimates. One possible use of this calculator might be in highlighting those patients who are unlikely to have a good outcome from amputation. For example, an underweight 85-year-old patient with sepsis who would need an above knee amputation would have a low chance of surviving amputation. Rather than intervening but with a high chance of prolonged morbidity and ultimately death, it may be better to consider palliative management, having now identified them accurately with this prognostic model.

Ten percent of patients returned to theatre during their index admission. This is quite a high proportion, and it would have been useful to examine the reasons for these returns to theatre. Unfortunately, no detail is given in the dataset so some of these patients will have had a minor debridement procedure while some will have had a major revision of amputation level. This may be the reason why it was difficult to generate a model with good discriminatory power for this outcome (Supplementary Table 4).

There are some indications that the medical management of the patients in this study was not optimal, with only 71% and 70% of patients being treated with antiplatelet or statin therapy respectively. The recent Global Vascular Guidelines on the management of chronic limb-threatening ischaemia give a level 1A recommendation to both of these,[27] so there is clearly room for improvement in this patient cohort, though these rates were far better than the rates of 39% and 11% respectively revealed by a recent prospective study of patients with peripheral arterial disease in the UK.[28] Of note, although statin use was associated with reduced mortality on univariate analysis, use of antiplatelet agents had no significant effect on any measured outcome.

Previous procedures to the amputated limb reduced mortality rates. While it is possible that having had previous procedures is simply a surrogate for 'fitness' in some way, it may also be that intervention to facilitate healing at a trans-tibial rather than trans-femoral level might have multiple benefits, both in terms of improved short-term outcomes and also in terms of the improvement in long-term functional outcomes. Supporting this hypothesis is the fact that 51% of patients with a previous procedure had a trans-tibial amputation, whereas only 43% of patients without a previous procedure had a trans-tibial amputation. While it is possible that some of the effect seen for trans-tibial amputation is due to unmeasured confounding, the association was strong even when all measured confounders were taken into account in multivariate modelling (adjusted odds ratio for in-hospital mortality 0.61, 95% C.I. 0.52-0.72).

Some of the effects seen in the univariate analysis highlight the importance of confounder correction using multivariate analysis or careful matching of patient groups. For example, examining the univariate analysis it appears that smoking is protective and beta-blockers are strongly associated with an increased risk of death. These effects are almost certainly artefacts caused by confounding. Indeed, the mean age of smokers was 62 whereas that of non-smokers was 70. Likewise, 60% of those on beta-blockers had a history of ischaemic heart disease, whereas only 30% of those not on a beta-blocker had a history of ischaemic heart disease.

Strengths of this work include the large, national database used, the rigorous statistical methods used both to handle missing data and also the information criterion approach to reduce the chances of over-fitting. The model we have presented has shown discrimination which improves on the previously published models (Figure 1).

Limitations of the study include the fact that the case completion rate in the NVR is known to be only around 60%.[29] This is a dramatic improvement over the situation 10 years ago, when only half this number of cases was entered.[30] The UK National Vascular Registry reports for the past two years have highlighted the fact that case ascertainment rates vary widely between Vascular Networks.[29,31] We can therefore be optimistic that much of the missing data relates largely to institutional and administrative factors rather than patient-related factors, but we must acknowledge the potential that the non-submitted cases might be systematically different from submitted cases, introducing bias into our results. In addition to missing cases, there was also a degree of missing data items within otherwise completed cases. However it must also be stressed that given the size of the database, even in cases where up to 50% of values are missing for a parameter, there will still be data from around 5000 (or more) cases. This, together with the rigorous multiple imputation methodology (the gold-standard method for handling missing data in clinical research), [32] gives us confidence that the results are valid. Sensitivity analysis using only complete cases gave very similar results (Table 2), so there is no evidence that these missing values have introduced significant bias.

Validation of data within the NVR is also lacking. This is a general criticism of registry-based studies, as to our knowledge, no national registry of major lower limb amputation cases has been rigorously validated. The Swedish Vascular registry (SwedVasc) and the Hungarian registry have been validated, although the former only for aortic aneurysm repair and carotid surgery while the latter also for infra-inguinal arterial reconstruction.[33,34] Plans are in place for a validation exercise of the UK NVR in 2020, but this also may not include the major lower limb amputation subset.

A further weakness of this study is due to limitations of the data recorded in the NVR. For example it is increasingly recognised that frailty is an important risk factor for peri-operative complications, including mortality.[35] Dependent functional status has been shown in other work to be important for predicting mortality in patients undergoing amputation.[5,7] However, until recently no measure of frailty or functional status has been recorded in the NVR. A measure of frailty has recently been added to the NVR dataset, which will allow further investigation of this factor in the future.

We have modelled in-hospital mortality, as that is the audit standard within the UK Vascular Registry. Unfortunately, this is different from many other national audit databases such as SwedVasc, which reports 30-day mortality. Inconsistency in outcome reporting presents difficulties for clinical audit and research, as it makes pooling of information between studies (meta-analysis) challenging. Efforts are underway to develop Core Outcome Sets for patients undergoing major lower limb amputation for complications of peripheral vascular disease.[36]

Several of the predictive factors we found are similar to those found in previous work. Increasing age was found to be an independent predictor of mortality in almost all previous studies, including this one. Emergency admission and level of amputation were also found to be predictive of mortality in several other studies, including work from large administrative databases in Japan and the USA.[6,7] Evidence of systemic sepsis in the form of a raised white cell count has also been identified as a significant factor in previous studies.[2,5] In contrast, bilateral procedures have not been previously shown in multivariate analysis to have a worse outcome than unilateral procedures, and increased patient weight has never been identified as an independent protective factor previously.

Further studies are needed to identify whether attempts to modify any of the factors have a clinically relevant impact on outcomes. Firstly, improvements might be made through quality improvement programmes designed to facilitate earlier identification and treatment of patients for whom further attempts at limb salvage are at high risk of failure. Improved shared decision-making using risk quantified by these data should be encouraged, perhaps supported by a decision aid.[37] Secondly, there are more speculative options which would require testing in prospective interventional studies. One of these is a proposed intervention to facilitate healing at a more distal level, as both prior procedures to the amputated limb and below knee operations appear to have a protective role. Increased patient weight and serum albumin have similar protective effects, so it is possible that pre-operative dietary intervention or other 'pre-habilitation' might also be helpful for patients with stable but un-reconstructable arterial disease. There is increasing interest into the putative benefits of 'pre-habilitation', with multiple on-going studies,[38] though little concrete evidence of benefit at this time.[39]

Further work is also needed to externally validate the predictive model. The importance of this was highlighted within Vascular Surgery recently with the publication of the draft National Institute for Health and Care Excellence (NICE) guidelines for the treatment of Abdominal Aortic Aneurysm,[40] which found that none of the models for that patient group which had been subjected to external validation were found to have good discriminatory power. The NICE panel also suggested that the literature on risk scoring in abdominal aortic aneurysm repair reports several un-validated risk scores, and concluded that there is no justification to develop further models in this context, until the external validity of existing ones is assessed. The situation for major limb amputation is somewhat different, with very few available models. Those which do exist are difficult to validate in the UK as they use parameters which are not routinely recorded in the NVR. We are therefore optimistic that the model we have developed has the potential to contribute to improvement of outcomes for patients with chronic limb-threatening ischaemia. Work on validating the model is planned for next year once data from the next two years is available.

In conclusion, we have identified independent risk factors for mortality and morbidity following major lower limb amputation and developed a prognostic model for in-hospital mortality with good predictive power. Important next steps include further external validation, and if supported, the development of quality improvement programmes which focus on modification of the factors we have identified, and adjustment of published surgical outcomes using this model.

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Disclosures

None

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Tables

Table 1: Baseline characteristics of patients undergoing major lower limb amputation in the UK National Vascular Registry.

Parameter	**Value** (N = 9549)	**Number** **missing (%)**
Age (median (IQR))	70 (60—78)	5 (0)
Sex (Male : Female)	6729 : 2820	0 (0)
Hospital type (teaching : non-teaching)	4544 : 5005	0 (0)
Emergency admission (N (%))	7489 (78.4)	0 (0)
Comorbidities (N (%))		
Diabetes	5065 (53.1)	
Ischaemic heart disease	3788 (39.7)	
Congestive heart failure	1004 (10.5)	
Chronic lung disease	1939 (20.3)	17 (0)
Chronic kidney disease	1968 (20.6)	
Hypertension	5812 (61.0)	
Stroke	1085 (11.4)	
Smoking (Never : Ex : Current)	1948 : 4721 : 2850	30 (0)
Pre-operative blood tests (median (IQR))		
White cell count (10^9 cells/L)	11.7 (9.0—15.4)	14 (0)
Haemoglobin (g/L)	112 (97—148)	3416 (36)
	136 (133—139)	38 (0)

Sodium (mmol/L) Potassium (mmol/L) Creatinine (μmol/L) Albumin (g/L)	4.5 (4.1—4.9) 81 (61—118) 30 (24—35)	18 (0) 11 (0) 2824 (30)
Abnormal ECG (N (%))	3672 (42.9)	988 (10)
ASA grade (1 : 2 : 3 : 4 : 5)	90 : 756 : 6164 : 2462 : 75	2 (0)
Indication (N (%))*		16 (0)
Acute Limb Ischaemia	1563 (16.4)	
Chronic Limb Ischaemia	1981 (20.8)	
Neuropathy	140 (1.5)	
Tissue Loss	3567 (37.4)	
Uncontrolled Infection	2129 (22.3)	
Trauma	94 (1.0)	
Aneurysm	59 (0.6)	
Pre-operative medications (N (%))		
Antiplatelet agent	6783 (71.1)	
Statin	6701 (70.2)	3 (0)
Beta-blocker	2560 (26.8)	
ACE-inhibitor / ARB	3035 (32.0)	
Weight (median (IQR))	75 (63—87)	2607 (27)

Data are presented as median with interquartile range (IQR) for continuous variables and number (percentage) for categorical variables, apart from sex, hospital type, smoking status *and ASA grade, where numbers in each category are separated by colons. ACE – Angiotensin converting enzyme. ARB – Angiotensin II receptor blocker. Abnormal ECG is a field in the NVR with only two options – normal or abnormal.*

** Amputations for malignancy are not recorded in the National Vascular Registry.*

Table 2: Univariate analysis showing odds ratios of being discharged alive according to different risk factors for patients undergoing major lower limb amputation in the UK National Vascular Registry.

Parameter	Multiple Imputation			Complete Case Analysis	
	O.R.	95% C.I.	P-value	O.R.	95% C.I.
Age (per 10 year $\uparrow$)	0.763	0.720—0.809	<0.0001	0.764	0.721—0.810
Sex (Male vs. Female)	1.241	1.070—1.439	0.004	1.241	1.070—1.439
Hospital type (teaching : non-teaching)	1.034	0.899—1.190	0.637	1.034	0.899—1.190
Emergency admission	0.263	0.203—0.342	<0.0001	0.263	0.203—0.342
Previous intervention on same side	1.617	1.406—1.861	<0.0001	1.618	1.406—1.861
Below knee amputation vs. higher level	2.216	1.907—2.575	<0.0001	2.216	1.907—2.575
Comorbidities (Y : N)					
Diabetes	1.069	0.930—1.230	0.349	1.069	0.930—1.230
Ischaemic heart disease	0.634	0.551—0.730	<0.0001	0.635	0.552—0.731
Congestive heart failure	0.478	0.397—0.576	<0.0001	0.479	0.398—0.577
Chronic lung disease	0.690	0.588—0.810	<0.0001	0.690	0.588—0.811
Chronic kidney disease	0.477	0.411—0.555	<0.0001	0.477	0.411—0.556
Hypertension	0.867	0.750—1.003	0.054	0.868	0.750—1.003
Stroke	0.785	0.640—0.963	0.021	0.785	0.640—0.963
Smoking – Current	1.208	1.031—1.415	0.019	1.206	1.030—1.413
Pre-operative blood tests					
White cell count (per 10^9 cells/L $\uparrow$)	0.968	0.961—0.975	<0.0001	0.968	0.961—0.975
	1.005	0.996—1.014	0.307	1.005	0.996—1.014

Haemoglobin (per g/L ↑)	0.995	0.980—1.010	0.507	0.995	0.980—1.010
Sodium (per mmol/L ↑)	0.993	0.924—1.069	0.860	0.994	0.924—1.069
Potassium (per mmol/L ↑)	0.973	0.968—0.977	<0.0001	0.973	0.968—0.977
Creatinine (per 10 μmol/L ↑)	1.061	1.051—1.072	<0.0001	1.062	1.051—1.072
Albumin (per g/L ↑)					
Abnormal ECG	0.411	0.353—0.478	<0.0001	0.400	0.343—0.467
ASA grade (per grade ↑)	0.248	0.219—0.282	<0.0001	0.248	0.219—0.282
Pre-operative medications					
Antiplatelet agent	1.113	0.957—1.295	0.166	1.113	0.957—1.295
Statin	1.258	1.086—1.459	0.002	1.259	1.086—1.459
Beta-blocker	0.718	0.619—0.834	<0.0001	0.719	0.619—0.834
ACE-inhibitor / ARB	1.169	1.002—1.363	0.047	1.169	1.002—1.364
Weight (per 10kg ↑)	1.085	1.042—1.129	<0.0001	1.088	1.043—1.134

The last two columns present a sensitivity analysis using complete cases only. Numbers greater than one indicate greater odds of being discharged alive. O.R. – Odds Ratio. C.I. – Confidence Interval. ACE – Angiotensin converting enzyme. ARB – Angiotensin II receptor blocker. The ↑ symbol is used to indicate an increase in value, for example 'per 10 year ↑' indicates that the odds ratios are those associated with a ten-year increase in age.

Caption for Figure

Figure 1: ROC curve for UKAmpRisk, the prognostic model developed here, for patients undergoing major lower limb amputation in the UK National Vascular Registry, with best estimates of the VAM,[7] VBHOM[2,3] and NSQIP models.[5] Some predictive variables for VAM, VBHOM and NSQIP models are not available in the National Vascular Registry.